Responses to Major Comments on Technical Support Document

Public Health Goal

For

Diquat

In Drinking Water

Prepared by

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for diquat as discussed at the PHG workshop held on November 5, 1999, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.org. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

U.S. Environmental Protection Agency, Office of Water

Comment: "The California draft PHG for diquat is 0.15 mg/L/day (15 ppb) based on 20 percent relative source contribution from drinking water. This value is based on the adequate toxicity data and supported by the selection of the chronic dietary rat study for the calculation of the PHG. Both the selected NOAEL of 0.22 mg/kg/day for lens opacity and cataracts from this study, and the applied uncertainty factor of 100 for this endpoint are adequate."

Response: The Public Health Goals (PHG) units are mg/L (or ppb), but not mg/L/day. No change was requested, or made.

University of California, Riverside

Comment: In the Introduction, "Describe how diquat is "closely related" to paraquat. The status of paraquat as a toxic substance differs sharply from that of [diquat] with respect to disposition and adverse health effects."

Response: The Introduction's description of diquat and paraquat as closely related mentions that they are both quaternary bipyridylium herbicides, have similar uses and have the same mechanisms of herbicidal action. We agree that the toxic effects of paraquat and diquat differ because of different tissue uptake patterns, which are discussed later, but the chemical properties and herbicidal uses are being discussed in this section.

Comment: "P2, Phys Chem. How is the reader to interpret the last sentence related to "degradation, limit its biological activity, and decrease its environmental mobility." Since the PHG is at issue, these 3 factors should be clarified since they are determinants of environmental persistence and human exposure. The issue of time should be linked with quantity."

Response: This section merely describes physical properties of diquat. The significance of soil binding and other aspects of environmental persistence are briefly discussed on pp. 3-4, under Environmental Occurrence and Exposure, but the basic point in this section was that the tight binding of diquat to soil decreases its availability for many environmental interactions. No quantitative evaluation of the effects of the physical-chemical interactions (soil binding coefficients, degradation rates and half-life, etc.) on exposure to diquat is needed in the PHG document because these documents are not intended to provide complete characterizations of risk from environmental exposures.

Comment: "P2, Production. The statement about HSDB, 1998 seems to be incomplete. Use persists after 1982. What is the relationship between this statement and "California use of diquat…?""

Response: No recent information on production of diquat was available, whereas there was excellent recent information available on California usage of diquat. We do not know where the diquat used in California is manufactured, but it did not seem necessary to query the pesticide registrant about these details for our purposes in the water program.

Comment: "P3, ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE. This section addresses Air, Soil, Water, Food and Other Sources. It does not provide an estimate of human exposure. The section should be retitled or amended to include an estimate of human exposure related to present use practices."

Response: Evaluation of risk from present use practices of pesticides is the responsibility of the California Department of Pesticide Regulation (DPR), and this kind of information should be sought in the Risk Characterization Documents for pesticides prepared by DPR. PHG documents are primarily oriented toward discussion of drinking water issues. Noting that there are environmental residues of diquat, the conditions under which these occur in different media where the diquat might be available to humans, and stating representative concentrations, where available, comprises the intended scope of this section. In our opinion, this limited scope is consistent with the present title of the section.

Comment: "P3, Air. Is it sufficient to say that "droplet settling would normally be the predominant removal mechanism (HSDB, 1998)" from air. Is there any use practice in which particle deposition is not the "predominant mechanism?"

Response: Point well taken. The statement has been changed to "is the predominant removal mechanism." An extended discussion on use practice would not be within the scope of the PHG document.

Comment: "P4, Air. Hazard of drift should be elaborated. How is drift defined in this document? Is the drift exposure the result of misapplication or normal use?"

Response: We acknowledge the reviewer's interest in exposure issues, particularly spray drift, and agree that offsite drift of pesticide sprays may be of great importance for pesticide use and exposure analysis. The term "spray drift" was intended to refer to spread of aqueous droplets or particulate matter from normal use of diquat, irrespective of the method of production or application of that spray. However, discussion of these issues is not within the scope of the PHG document.

Comment: "The Spray Drift Task Force is not a USEPA to my knowledge. Text should be clarified."

Response: Agreed. The Spray Drift Task Force is a pesticide industry committee convened by U.S. EPA pursuant to FIFRA Section 3(c)(2)(B)(ii) but is not part of U.S. EPA. This has been clarified in the text.

Comment: "P5, METABOLISM AND PHARMACOKINETICS. Complete as written."

Response: No change needed.

Comment: "P7, TOXICOLOGY. Time factor should be clearly stated in this PHG document. With respect to Acute Toxicity: Is the response following a single dose or short term dosing. Reference the situation which presently exists in the pesticide regulatory arena where single dose and short term dosages are not distinguished. The regulatory community is the first issue (the public generally considers that acute refers to the condition of the "victim" rather than the time interval of exposure!)."

Response: The intent of this comment is not clear. The references cited in the animal Acute Toxicity section describe single-dose effects of diquat, and there is no discussion of pesticide regulations or the regulatory community; the time factors of these experiments are straightforward. Acute refers in the discussion to short-term exposures, not to duration of any resulting symptoms. No changes appear to be needed.

Comment: "One need not look far! Page 13 Acute Toxicity includes "Severe skin injuries…from prolonged acute or repeated exposures…." I do not think so."

Response: The phrase "short-term" has been substituted for the phrase "prolonged acute" in the PHG document. Our wording referred to a case described by Manoguerra (Clin. Toxicol. 28:107-110, 1990) who reports "A case of full thickness burns of the feet requiring skin grafting [that] occurred following prolonged exposure to the soles of the feet to diquat dibromide." The worker spilled formulated diquat into his boots, and noticed a burning sensation in one foot that night. He attempted to swab the boots dry the next day, and wore them till noon when his feet became extremely painful; severe complications followed with no more exposure." Other cases describe injuries to workers caused by repeated spilling of diquat or paraquat formulations on the hands or other skin areas over rather short time periods. We see no reason for dispute about the potential for skin injuries following short-term exposures to bipyridyl pesticides.

Comment: "P8, Dermal application. Would it not be more appropriate to refer to dose as amount per unit skin area. The text includes a disclaimer related to "not a systemic effect," but this is not adequate."

Response: Yes, it is preferable to describe dermal doses in terms of amount per unit area and applied concentration, as well as on a body weight basis. Of the two dermal studies evaluated for this toxicity summary, one provided the applied concentration (which is stated in the PHG document), the other did not, and neither stated the area. This uncertainty does not affect the PHG, which is not based on this effect or these studies.

Comment: "P9 Reproductive/Developmental. The NOAEL for systemic toxicity in the rat from the Hodge (1990) study was 4 mg/kg-day in adult and 1.6 mg/kg-day in pup. Other reported values were similar. It would be helpful to readers and to persons engaged in risk management to have the results of these studies presented in a tabular form. The conclusion that "a weak indication of developmental effects at 1 mg/kg-day" should be elaborated in greater detail (particularly in view of the disparity between the DPR and U. S. EPA conclusions."

Response: In the Hodge (1990) study, multiple toxic effects were noted at the LOEL doses; multiple effects at slightly higher doses were observed in five other reproductive/developmental studies (three in Wistar rats, one in rabbits, and one in mice). It seemed unnecessary to tabulate all these supporting data because they are well described in text and are not used for deriving the PHG, which is based on lens opacities in rats and dogs at still lower doses. The data from Hodge (1989) which was described as "a weak indication of developmental effects at 1 mg/kg-day" are already tabulated, and this is the most extensively described study in the entire document.

Comment: "P12. Clarification of NOAEL for lens opacities must be provided. There is apparent uncertainty regarding dosage. There is not sufficient information for an informed reviewer to use to make judgement about suitability of an end point acknowledged to be of no statistical significance (paragraph one)."

Response: The only uncertainty regarding dose that we are aware of is in the Integrated Risk Information System (IRIS) file, which has mixed up the doses and concentrations. The study itself is clear, although the poor survival limits the statistical significance. As noted below by another reviewer, this study has data that appear appropriate for a benchmark analysis. Our plot of these data (not shown) indicates an acceptable straight-line relationship through zero dose on linear axes. If a benchmark were set at 5 percent animals responding, the corresponding dose is about 0.6 mg/kg; if it were set at 10 percent responses, it would be about 1.8 mg/kg. Because the next lower dose is only three-fold lower, at 0.22 mg/kg-day, we felt comfortable calling 0.22 mg/kg-day a NOAEL, and then using an uncertainty factor of 100 (10 for cross-species and 10 for human variability) to estimate a safe dose. We therefore decided to use the traditional LOAEL/NOAEL approach applied to the lower NOAEL of 0.22 mg/kg-day identified by DPR plus the minimum default uncertainty factor (UF) for an animal study, instead of the NOAEL of 0.58 mg/kg-mg/kg-day identified by U.S EPA. We acknowledge that other approaches were possible, but think that this is, at present, the most logical and appropriate methodology among the available choices.

Comment: "P13, Acute Tox. Dipyridyls is not a suitable classification with respect to human illness. Provide separate data and clearly differentiate paraquat and diquat."

Response: Most of the acute toxicity description in this section clearly differentiates between toxic effects of diquat and paraquat. Of the two references to dipyridyls, the first relates to use of mixed paraquat/diquat formulations in suicides, where the plural was necessary. The second relates to the potential for Parkinsonian-like effects. Both chemicals have been prominently mentioned in this literature, as cited. No change appears warranted.

Comment: "P14. Are the [statements] regarding genetic toxicity, developmental and reproductive toxicity, and immunotoxicity intended to indicate no evidence of [toxic]ity has been reported OR are the effects to be assumed? I suggest a rewrite."

Response: The intent of these comments was to indicate that there were no applicable studies and no evidence on human genetic toxicity, developmental and reproductive toxicity, and immunotoxicity of dipyridyl pesticides. The statement on genetic toxicity has been clarified. However, the other two statements (no information is available on developmental or reproductive toxicity in humans; no reports were found on immunotoxic effects in humans) seem straightforward and clear, and were not changed. There are no reports and no evidence of any such effects in humans.

Comments: Regarding the paragraph on Toxicological Effects in Humans, Carcinogenicity, “Are “Studies in animals negative?” Does “considered to be negative” carry a different message to a likely reader of this document?”

Response: There was a small increase in a rare tumor type (three osteosarcomas) in male rats at the highest dose tested. The results were marginally significant by a trend test. Both DPR and U.S. EPA considered the results to be not indicative of carcinogenicity. Our wording was intended to indicate that the decision involved professional judgement, which we continue to believe is worth noting. The PHG text has been changed to indicate that both DPR and U.S. EPA considered the results to be negative.

Comment: Regarding appropriateness of the data set selected for deriving the public health goal (PHG) and the supporting information, “With the exceptions noted above, data are generally appropriate.”

Response: No change requested.

Comment: In response to the question, “Do the data support the conclusions?” the reviewer replied, “The numeric result of dividing the daily dosage by a factor of 100 to obtain a NOAEL is correct, but the expression does not address the long-term nature of the experimental studies. Existing patterns of use can not result in exposures that are related to those used in the risk assessment.”

Response: Because diquat is rarely detected in drinking water, we agree that significant chronic exposures are unlikely, and no effects are expected from diquat in drinking water.

Comment: In response to the question, “Are there other improved methods?” the reviewer replied, “Not to my knowledge—excepting the comments in section 1. related to accurate reporting of data.”

Response: Point noted.

Comment: "It is important to consistently distinguish paraquat and diquat (especially pages 13 and 14). The discussion about MPTP and Parkinsonism is not appropriate in this document."

Response: We have gone over the document to identify passages that blur the distinction between the two chemicals, and found little to change. Several papers were cited on mixed herbicidal formulations containing both diquat and paraquat, in which specific toxic effects could not be clearly ascribed to only one of the constituents. The discussion of neurological symptoms resulting from diquat poisoning would not be complete, in our opinion, without mention of the MPTP/Parkinson oxidative damage hypothesis.

University of California, Davis.

Comment: "The data set chosen is appropriate, and adequately justified by supporting information."

Response: No change needed.

Comment: Regarding appropriateness of the methodology used, "Benchmark dose approach might have been better with the kind and quantity of data available."

Response: Yes, that would be possible, but benchmark methods were not used because we have no guidelines on how to apply them for this kind of data. A benchmark approach is described above in the responses to the comments from University of California, Riverside.

Comment: Other major/critical information that needs to be considered which may impact the proposed PHG: "None"

Response: No response needed.

Comment: Regarding description of uncertainties, "Use of rigid default values for Relative Source Contribution (RSC) that are totally arbitrary…is less than optimal; it creates an unnecessary problem that can, and should, be avoided." The reviewer goes on to recommend an RSC of .267 so the PHG will exactly agree with the state and federal maximum contaminant levels (MCLs).

Response: We do not agree that a PHG of 15 ppb represents an important difference from the established MCLs of 20 ppb. This is merely a rounding difference using our general approach of calculating PHGs to two significant figures. Adjusting the RSC in order to agree exactly with the existing MCLs is too arbitrary and does not lend support to its use in this case or for other chemicals.

Comment: "There is a lot of confusion in this document about aerosols, inhalation toxicology, and inhalation exposure assessment. Some clarification of assumptions might help. For example, the concept that higher exposure can occur in the shower than from drinking water, first suggested by Tom McKone of LLNL, refers to volatile solvents or gasses like radon, which are air-stripped at almost 100 percent efficiency from water droplets in the shower. It does not pertain to non-volatile agents like Diquat. Actual exposure to respirable aerosols in the shower will depend on particle (droplet) size, temperature and relative humidity, but should be low. Assumptions about extent of exposure in the shower setting in the Diquat risk assessment should be clarified. In addition, respirable aerosols are not 10 um MMAD (PM_{10}) as suggested on page 5, but more likely are analogous to $PM_{2.5}$. Can the fine particle exposure in a shower be estimated?"

Response: There are no data to estimate exposure from respirable aerosol particles in showering. This route is mentioned because of the much higher toxicity of diquat by inhalation than by oral or dermal routes which has the potential to result in a disproportionately high effect from a very small fractional uptake. However, we did not intend to imply that the exposure to diquat in the shower was greater than that from drinking water. Because of the paucity of information about this possible exposure pathway, its description in the PHG document has been shortened and simplified to avoid this confusion.

Comment: "The rationale for choosing a LOAEL//NOAEL approach to standard setting in preference to the Benchmark dose approach, which is generally considered to be superior for noncarcinogen risk assessment, should be explicitly stated and justified."

Response: We do not consider it necessary to discuss benchmark methods in the PHG documents. However, we agree that OEHHA should consider these methods further.

Comment: "Page 5, paragraph 1. The discussion of transport mechanisms tacitly assumes passive transport. This is not true for paraquat in the lung, where active transport mechanisms exist in epithelial cells and are responsible for the high toxicity of paraquat for lung cells. This is why the toxicity of paraquat is so much greater than that of Diquat, so this is not a trivial issue in this context."

Response: We agree, but a statement about paraquat active transport seems out of place in the first paragraph. A notation on this point has been inserted into the fifth paragraph on this page, in which lung uptake of diquat is discussed.

Comment: "Page 5, paragraph 5. Ten micron [sic, micrometer is correct] particles are not respirable aerosols. That is why we now have a $PM_{2.5}$ standard. Particles greater than 2-4 um MMAD will not reach the alveolae, and to assume 100 percent penetration to the alveolae we would require particles in the size range 0.2-2 um. Depending on the size of the aerosol, 70 percent exposure to respirable-sized particles may be much too high an estimate if all of the PM_{10} fraction is included. This paragraph needs rewriting and clarification of the assumptions therein."

Response: Agreed, discussion simplified.

Comment: "Page 8, paragraph 3. A NOEL of 0.1 µg/L of Diquat aerosol corresponds to a concentration of 100 $\mu g/M^3$ in air. This is a very high concentration for a real aerosol exposure. Has the subsequent concern about aerosol concentrations in showers taken these data into account? How? These assumptions should be clarified."

Response: No specific calculations are presented because no information on aerosol concentrations and diameters produced in showering were available. Our concern about aerosol exposures relates to the fact that the subchronic inhalation LOAEL is approximately 0.02 mg/kg-day, whereas the subchronic oral LOAEL is 5 mg/kg-day. This apparent 250-fold greater potency by the inhalation route indicates a potential for significant inhalation exposures despite the low fractional uptake, which we have chosen to take note of.

Comment: "Page 10, paragraph 1. Are the “negative findings” of US EPA (in contrast to DPR) based upon the apparent lack of dose-response in the cited data? If so, this should be stated, and commented upon."

Response: We do not know why U.S. EPA chose to conclude, "nothing remarkable was observed in the low-dose (1 mg/kg/day) group," while DPR noted a significant increase in delayed ossification and malformed fetuses at that dose. We agree that there is a poor dose-response, which we have described as "a weak indication of developmental effects at 1 mg/kg-day." Stating our own conclusion seemed better than trying to infer U.S. EPA's rationale.

Comment: "Page 16, paragraph 3. The use of an arbitrary default value for RSC seems to depend on a rigid protocol guideline and an assumption of the relative importance of aerosol exposures as a source. Neither the choice of default nor the importance of aerosol exposure is justified in this document. To justify the weighting of the aerosol exposure as a source term we need to know the particle size concentration, and the duration of aerosol exposures that were assumed in order to justify this source apportionment. These data are not presented in this document. This is a significant shortcoming of the risk assessment. This calculation should be shown. If the apportionment to aerosol exposure is all based

on exposure in showers, the assumptions should be spelled out. If field exposures are also included, is this appropriate for a PHG?"

Response: We agree that assuming a large contribution from showering would be unwarranted, because of the lack of any data on this pathway. While the discussion did not explicitly claim a large inhalation contribution, that inference might logically be made from the discussion provided. Therefore we have reworded this passage to confirm that this possible exposure is likely to be small. An RSC of 0.2 is the standard default for a non-volatile pesticide with significant food sources, and remains unchanged.

Comment: "Page 17, paragraph 3. The low volatility of Diquat and low exposure to Diquat in the vapor phase is acknowledged. Why wasn't 0.4 or 0.8 chosen as the RSC? This needs to be discussed more completely, and the underlying assumptions exposed."

Response: Some of the tolerances for diquat in food are relatively high, up to 1 ppm for processed potatoes, 2 ppm for fish, and 20 ppm for shellfish (although the incidence of significant residues found in food is low). On the other hand, diquat is not commonly found in finished drinking water because of its tight binding to suspended sediment, which is filtered out. Therefore the default factor of 0.2 for a pesticide for which the major exposure source is likely to be food was chosen. This is a significant source of uncertainty in the calculation, which has now been noted in the Risk Characterization section.